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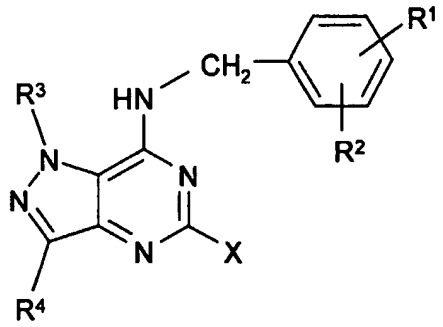
(54) Title: PROCESS FOR THE PREPARATION OF A PYRAZOLO[4,3-D]PYRIMIDINE DERIVATIVE

(57) Abstract: The invention relates to a process for the preparation of [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl-methoxy]acetic acid and intermediates thereof.

Process for the preparation of a pyrazolo[4,3-d]pyrimidine derivative

The invention relates to a process for the preparation of [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl-methoxy]acetic acid.
This substance specifically inhibits cGMP phosphodiesterase (PDE V).

Compounds of the formula I



I

in which

R^1 and R^2	are each, independently of one another, H, A, OH, OA or Hal,
R^1 and R^2	together are alternatively alkylene having 3-5 carbon atoms, $-O-CH_2-CH_2-$, $-CH_2-O-CH_2-$, $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$,
R^3 and R^4	are each, independently of one another, H or A,
X	is R^5, R^6 or R^7, each of which is monosubstituted by R^8,
R^5	is linear or branched alkylene having 1-10 carbon atoms, in which one or two CH_2 groups may be replaced by -CH=CH- groups, O, S or SO,
R^6	is cycloalkyl or cycloalkylalkylene having 5-12 carbon atoms,
R^7	is phenyl or phenylmethyl,
R^8	is COOH, COOA, $CONH_2$, CONHA, $CON(A)_2$ or CN,
A	is alkyl having from 1 to 6 carbon atoms, and

Hal is F, Cl, Br or I,
and physiologically acceptable salts and solvates thereof are known.

Other pyrimidine derivatives are known, for example, from EP 201 188 or WO 93/06104.

The compounds of the formula I and their salts have very valuable pharmacological properties and are well tolerated.
In particular, they exhibit specific inhibition of cGMP phosphodiesterase (PDE V).

Quinazolines having a cGMP phosphodiesterase-inhibiting activity are described, for example, in J. Med. Chem. 36, 3765 (1993) and ibid. 37, 2106 (1994).

The biological activity of the compounds of the formula I can be determined by methods as described, for example, in WO 93/06104.
The affinity of the compounds according to the invention for cGMP and cAMP phosphodiesterase is determined by measuring their IC_{50} values (concentration of the inhibitor needed to achieve 50% inhibition of the enzyme activity).
The determinations can be carried out using enzymes isolated by known methods (for example W.J. Thompson et al., Biochem. 1971, 10, 311).
The experiments can be carried out using a modified batch method of W.J. Thompson and M.M. Appleman (Biochem. 1979, 18, 5228).

The compounds are therefore suitable for the treatment of illnesses of the cardiovascular system, in particular cardiac insufficiency, and for the treatment and/or therapy of potency disorders (erectile dysfunction).

The use of substituted pyrazolopyrimidinones for the treatment of impotence is described, for example, in WO 94/28902.

The compounds are effective as inhibitors of phenylephrine-induced contractions in corpus cavernosum preparations of rabbits. This biological

action can be demonstrated, for example, by the method described by F. Holmquist et al. in J. Urol., 150, 1310-1315 (1993).
The inhibition of the contraction demonstrates the effectiveness of the compounds according to the invention for the therapy and/or treatment of potency disorders.

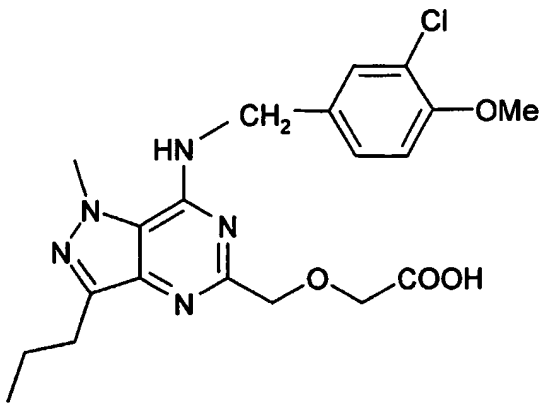
The compounds of the formula I can be employed as medicament active ingredients in human and veterinary medicine. They can furthermore be employed as intermediates in the preparation of further medicament active ingredients.

[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]-pyrimidin-5-ylmethoxy]acetic acid has proven to be a highly suitable and highly effective substance. This substance has not only a very good action in the treatment of erectile dysfunction, but can also advantageously be employed in the treatment of pulmonary hypertension.

Since this substance is very highly promising, its preparation is of extremely high interest. The preparation of this class of substances is described, for example, in EP 463756 and EP 526004.
Processes for similar intermediates are disclosed, for example, in EP 819678.

There is therefore considerable interest in finding an improved process for the preparation of [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy]acetic acid.
The object of the present invention was therefore to find a novel and effective synthesis variant for the said PDE V inhibitor.

The invention therefore relates to a process for the preparation of [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]-pyrimidin-5-ylmethoxy]acetic acid



where

a) 1-methyl-3-propyl-4-amino-5-aminocarbonyl-1*H*-pyrazole ("Z6") is reacted with diglycolic anhydride to give [(5-aminocarbonyl-1-methyl-3-propyl-1*H*-pyrazol-4-ylcarbamoyl)methoxy]acetic acid ("Z7") or

a') "Z6" is reacted with a compound of the formula ("Z7B")

$$L\text{-}CO\text{-}CH_2\text{-}O\text{-}CH_2\text{-}COOA \qquad \text{"Z7B"}$$

where L is Cl, Br, OH, SCH_3 or a reactive esterified OH group, and

A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms or benzyl,

to give [(5-aminocarbonyl-1-methyl-3-propyl-1*H*-pyrazol-4-ylcarbamoyl)-methoxy]acetic acid A ester ("Z7B"),

where

A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms or benzyl,

subsequently

b) "Z7" or "Z7B" is converted into (7-oxo-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy)acetic acid ("Z8") by cyclisation, then

c) "Z8" is converted into (7-oxo-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]-pyrimidin-5-ylmethoxy)acetic acid A ester ("Z9"),

where

A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms or benzyl,

subsequently

d) "Z9" is converted into (7-chloro-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-ylmethoxy)acetic acid A ester ("Z10"),
where
A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms
or benzyl,
by oxygen-chlorine exchange,
subsequently
e) "Z10" is reacted with 3-chloro-4-methoxybenzylamine to give [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]-pyrimidin-5-ylmethoxy]acetic acid A ester ("Z11"),
where
A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms
or benzyl,
and finally
f) "Z11" is hydrolysed to give [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy]acetic acid ("Z12").

The starting materials for the preparation of [7-(3-chloro-4-methoxy-benzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl-methoxy]acetic acid are, in addition, prepared by methods known per se, as described in the literature (for example in the standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), to be precise under reaction conditions which are known and suitable for the said reactions. Use can also be made here of variants which are known per se, but are not mentioned here in greater detail.
The aminoamide "Z6" is known from the literature.

The reaction of "Z6" with diglycolic anhydride to give "Z7" is carried out in the presence or absence of an inert solvent at temperatures between about -20 and about 150°, preferably between 20 and 100°. The yields are about 90%.

The reaction of "Z6" with a compound of the formula "Z7B" is likewise carried out in the presence or absence of an inert solvent at temperatures between about -20 and about 150°, preferably between 20 and 100°. If L is a reactive esterified OH group, this is preferably alkylsulfonyloxy having 1-6 carbon atoms (preferably methylsulfonyloxy) or arylsulfonyloxy having 6-10 carbon atoms (preferably phenyl- or p-tolylsulfonyloxy, furthermore also 2-naphthalenesulfonyloxy).

Examples of suitable inert solvents are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichloroethylene, 1,2-dichloroethane, carbon tetrachloride, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether, ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide, N-methylpyrrolidone or dimethylformamide (DMF); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate, or mixtures of the said solvents.

The conversion of "Z7" into "Z8" is carried out in an aqueous solution of an alkali metal hydroxide or alkaline earth metal hydroxide at temperatures between about -20 and about 150°, preferably between 20 and 120°, very particularly preferably between 80° and 110°. The cyclisation is preferably carried out in aqueous NaOH or KOH solution. The yields are about 93%.

The esterification of "Z8" to "Z9" is carried out by known methods at temperatures between about -20 and about 150°, preferably between 20 and 100°, using the corresponding alcohols. The yields are about 95%.

The conversion of "Z9" into "Z10" is preferably carried out using phosphorus oxychloride (analogously to Houben Weyl E9b/2) with addition of an organic base, such as N-ethyldiisopropylamine, triethylamine,

dimethylamine, pyridine or quinoline, at temperatures between about -20° and about 100°, preferably between 0° and 60°.

It is also possible to add an inert solvent, as indicated above. The yields are about 90%.

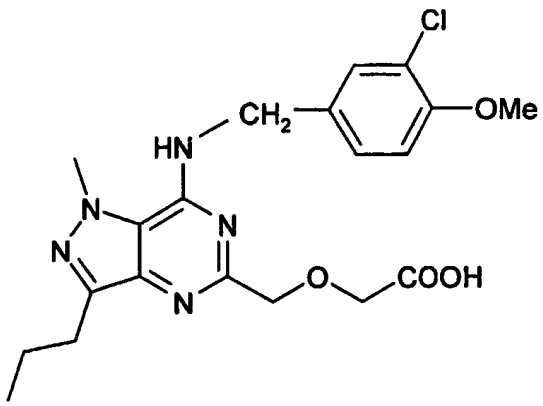
The reaction of "Z10" with 3-chloro-4-methoxybenzylamine to give "Z11" is carried out in the presence or absence of an inert solvent at temperatures between about -20 and about 150°, preferably between 20 and 100°.

The addition of an acid-binding agent, for example an alkali or alkaline earth metal hydroxide, carbonate or bicarbonate, or of another salt of a weak acid of the alkali or alkaline earth metals, preferably of potassium, sodium or calcium, or the addition of an organic base, such as triethylamine, dimethylamine, pyridine or quinoline, or of an excess of the amine component may be favourable. Suitable inert solvents are those mentioned above.

The hydrolysis of "Z11" to "Z12" can be carried out, for example, using NaOH or KOH in water, water/THF or water/dioxane at temperatures between 0 and 100°.

"Z12" can be converted into the associated acid-addition salt using a base, for example by reaction of equivalent amounts of the acid and the base in an inert solvent, such as ethanol, followed by evaporation. Suitable bases for this reaction are, in particular, those which give physiologically acceptable salts.
Thus, the acid of the formula I can be converted using a base (for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate) into the corresponding metal salt, in particular alkali metal salt or alkaline earth metal salt, or into the corresponding ammonium salt. Organic bases which give physiologically acceptable salts, such as, for example, ethanolamine, are also particularly suitable for this reaction.

The invention relates, in particular, to a process for the preparation of [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]-pyrimidin-5-ylmethoxy]acetic acid



where

a) diethyl oxalate is reacted with methyl propyl ketone to give ethyl 2,4-dioxoheptanoate ("Z1"),

subsequently

b) "Z1" is converted into 3-propyl-5-ethoxycarbonyl-1*H*-pyrazole ("Z2"),

then

c) "Z2" is converted into 1-methyl-3-propyl-5-carboxy-1*H*-pyrazole ("Z3") by methylation and hydrolysis,

subsequently

d) 1-methyl-3-propyl-4-nitro-5-carboxy-1*H*-pyrazole ("Z4") is obtained from "Z3" by nitration,

then

e) "Z4" is converted into the carboxamide 1-methyl-3-propyl-4-nitro-5-aminocarbonyl-1*H*-pyrazole ("Z5"),

subsequently

f) "Z5" is converted into 1-methyl-3-propyl-4-amino-5-aminocarbonyl-1*H*-pyrazole ("Z6") by reduction,

then

g) 1-methyl-3-propyl-4-amino-5-aminocarbonyl-1*H*-pyrazole ("Z6") is reacted with diglycolic anhydride to give [(5-aminocarbonyl-1-methyl-3-

propyl-1*H*-pyrazol-4-ylcarbamoyl)methoxy]acetic acid ("Z7") or

g') "Z6" is reacted with a compound of the formula ("Z7B")

$$L\text{-}CO\text{-}CH_2\text{-}O\text{-}CH_2\text{-}COOA \qquad \text{"Z7B"}$$

where L is Cl, Br, OH, SCH_3 or a reactive esterified OH group, and

A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms
or benzyl,

to give [(5-aminocarbonyl-1-methyl-3-propyl-1*H*-pyrazol-4-ylcarbamoyl)-methoxy]acetic acid A ester ("Z7B"),

where

A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms
or benzyl,

subsequently

h) "Z7" is converted into (7-oxo-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]-pyrimidin-5-ylmethoxy)acetic acid ("Z8") by cyclisation,

then

i) "Z8" is converted into (7-oxo-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]-pyrimidin-5-ylmethoxy)acetic acid A ester ("Z9"),

where

A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms
or benzyl,

subsequently

j) "Z9" is converted into (7-chloro-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-ylmethoxy)acetic acid A ester ("Z10"),

where

A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms
or benzyl,

by oxygen-chlorine exchange,

subsequently

k) "Z10" is reacted with 3-chloro-4-methoxybenzylamine to give [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]-pyrimidin-5-ylmethoxy]acetic acid A ester ("Z11"),

where

A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms
or benzyl,

and finally

l) "Z11" is hydrolysed to give [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy]acetic acid ("Z12").

Compounds "Z1" to "Z6" are known from the literature.

The invention furthermore relates to the novel intermediates

a) [(5-aminocarbonyl-1-methyl-3-propyl-1*H*-pyrazol-4-ylcarbamoyl)-methoxy]acetic acid;

b) [(5-aminocarbonyl-1-methyl-3-propyl-1*H*-pyrazol-4-ylcarbamoyl)-methoxy]acetic acid A ester,
where
A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms
or benzyl;

c) (7-oxo-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl-methoxy)acetic acid;

d) (7-oxo-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl-methoxy)acetic acid A ester,
where
A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms
or benzyl;

e) (7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl-methoxy)acetic acid A ester,
where
A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms
or benzyl;

f) [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy]acetic acid A ester,
where
A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms
or benzyl;

g) [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy]acetic acid,

and salts and solvates thereof.

The starting materials for the preparation of [7-(3-chloro-4-methoxy-benzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl-methoxy]acetic acid are, in addition, prepared by methods known per se, as described in the literature (for example in the standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), to be precise under reaction conditions which are known and suitable for the said reactions. Use can also be made here of variants which are known per se, but are not mentioned here in greater detail.

The term "solvates of the compounds of the formula I" is taken to mean adductions of inert solvent molecules onto the compounds of the formula I which form owing to their mutual attractive force. Solvates are, for example, mono- or dihydrates or alcoholates.

A is alkyl having 1-6 carbon atoms.
In the above compounds, alkyl is preferably unbranched and has 1, 2, 3, 4, 5 or 6 carbon atoms and is preferably methyl, ethyl or propyl, furthermore preferably isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, but also n-pentyl, neopentyl, isopentyl or hexyl.

Above and below, all temperatures are given in °C. In the following examples, "conventional work-up" means that water is added if necessary, the pH is adjusted, if necessary, to between 2 and 10, depending on the constitution of the end product, the mixture is extracted with ethyl acetate or dichloromethane, the phases are separated, the organic phase is dried over sodium sulfate and evaporated, and the product is purified by chromatography on silica gel and/or by crystallisation.

Mass spectrometry (MS): EI (electron impact ionisation) M^+
FAB (fast atom bombardment) $(M+H)^+$

Example 1

1.1 13.5 g of diglycolic anhydride are added at 15° to a solution of 20.5 g of 1-methyl-3-propyl-4-amino-5-aminocarbonyl-1*H*-pyrazole ("Z6") in 400 ml of dichloromethane, and the mixture is stirred for a further 1 hour. The mixture is subjected to conventional work-up, giving 32.5 g of [(5-aminocarbonyl-1-methyl-3-propyl-1*H*-pyrazol-4-ylcarbamoyl)methoxy]-acetic acid ("Z7").

1.2 A solution of 10.0 g of "Z7" and 3.9 g of NaOH in 217 ml of water is heated at 95° for 1.5 hours. The mixture is cooled and subjected to conventional work-up, giving 9 g of (7-oxo-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-ylmethoxy)acetic acid ("Z8").

1.3 0.3 ml of sulfuric acid (95-97%) is added to a solution of 7.0 g of "Z8" in 80 ml of ethanol, and the mixture is refluxed for 2 hours. The solvent is removed, and the mixture is subjected to conventional work-up, giving 7 g of ethyl (7-oxo-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy)acetate.

1.4 110 ml of phosphoryl chloride are added to 14.8 g of ethyl (7-oxo-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy)acetate, then 9.5 ml of N-ethyldiisopropylamine are added at 10° with stirring, and the mixture is stirred at 50° for a further 3 hours.
The solvents are removed, then ice-water is added, and the mixture is subjected to conventional work-up, giving 14 g of ethyl (7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy)acetate as an oil.

1.5a 3 g of ethyl (7-chloro-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-ylmethoxy)acetate and 1.9 g of 3-chloro-4-methoxy-benzylamine in 50 ml of dimethylformamide (DMF) are stirred at 60° for 12 hours in the presence of potassium carbonate. After filtration, the solvent is removed, and the mixture is subjected to conventional work-up, giving 4.6 g of ethyl [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy]acetate.

or 1.5b

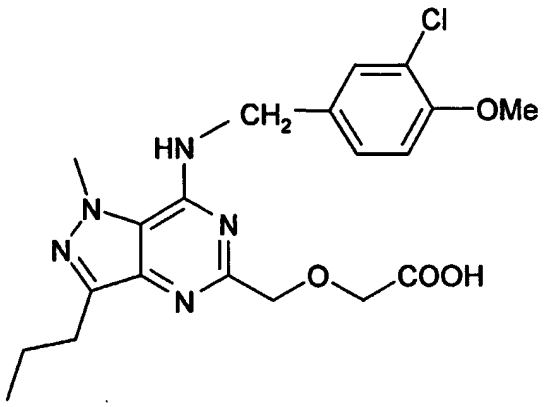
A mixture of 1.8 g of ethyl (7-chloro-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-ylmethoxy)acetate and 1.5 g of 3-chloro-4-methoxy-benzylamine in 20 ml of N-methylpyrrolidone is warmed at 110° for 4 hours. After cooling, the mixture is subjected to conventional work-up, giving 2.2 g of ethyl [7-(3-chloro-4-methoxybenzylamino-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy]acetate.

1.6 4.3 g of ethyl [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy]acetate are dissolved in 30 ml of tetrahydrofuran (THF), 10 ml of 10% NaOH are added, and the mixture is stirred at 60° for 8 hours. After 10% HCl has been added, the deposited crystals are separated off and recrystallised from methanol, giving 3.7 g of [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy]acetic acid.

Evaporation with the equivalent amount of ethanolamine in methanol gives [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]-pyrimidin-5-ylmethoxy]acetic acid, ethanolamine salt, m.p. 138°.

Patent Claims

1. Process for the preparation of [7-(3-chloro-4-methoxybenzyl-amino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy]acetic acid



where

a) 1-methyl-3-propyl-4-amino-5-aminocarbonyl-1*H*-pyrazole ("Z6") is reacted with diglycolic anhydride to give [(5-aminocarbonyl-1-methyl-3-propyl-1*H*-pyrazol-4-ylcarbamoyl)methoxy]acetic acid ("Z7") or

a') "Z6" is reacted with a compound of the formula ("Z7B")

$$L\text{-}CO\text{-}CH_2\text{-}O\text{-}CH_2\text{-}COOA \qquad \text{"Z7B"}$$

where L is Cl, Br, OH, SCH_3 or a reactive esterified OH group, and

A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms
or benzyl,

to give [(5-aminocarbonyl-1-methyl-3-propyl-1*H*-pyrazol-4-ylcarbamoyl)-methoxy]acetic acid A ester ("Z7B"),

where

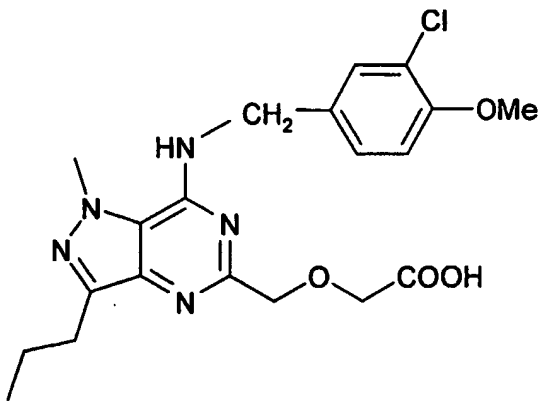
A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms
or benzyl,

subsequently

b) "Z7" or "Z7B" is converted into (7-oxo-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy)acetic acid ("Z8") by cyclisation, then

c) "Z8" is converted into (7-oxo-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]-pyrimidin-5-ylmethoxy)acetic acid A ester ("Z9"),
where
A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms
or benzyl,
subsequently
d) "Z9" is converted into (7-chloro-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-ylmethoxy)acetic acid A ester ("Z10"),
where
A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms
or benzyl,
by oxygen-chlorine exchange,
subsequently
e) "Z10" is reacted with 3-chloro-4-methoxybenzylamine to give [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]-pyrimidin-5-ylmethoxy]acetic acid A ester ("Z11"),
where
A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms
or benzyl,
and finally
f) "Z11" is hydrolysed to give [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy]acetic acid ("Z12").

2. Process for the preparation of [7-(3-chloro-4-methoxybenzyl-amino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy]acetic acid



where

a) diethyl oxalate is reacted with methyl propyl ketone to give ethyl 2,4-dioxoheptanoate ("Z1"),

subsequently

b) "Z1" is converted into 3-propyl-5-ethoxycarbonyl-1*H*-pyrazole ("Z2"),

then

c) "Z2" is converted into 1-methyl-3-propyl-5-carboxy-1*H*-pyrazole ("Z3") by methylation and hydrolysis,

subsequently

d) 1-methyl-3-propyl-4-nitro-5-carboxy-1*H*-pyrazole ("Z4") is obtained from "Z3" by nitration,

then

e) "Z4" is converted into the carboxamide 1-methyl-3-propyl-4-nitro-5-aminocarbonyl-1*H*-pyrazole ("Z5"),

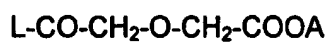
subsequently

f) "Z5" is converted into 1-methyl-3-propyl-4-amino-5-aminocarbonyl-1*H*-pyrazole ("Z6") by reduction,

then

g) 1-methyl-3-propyl-4-amino-5-aminocarbonyl-1*H*-pyrazole ("Z6") is reacted with diglycolic anhydride to give [(5-aminocarbonyl-1-methyl-3-propyl-1*H*-pyrazol-4-ylcarbamoyl)methoxy]acetic acid ("Z7") or

g') "Z6" is reacted with a compound of the formula ("Z7B")



"Z7B"

where L is Cl, Br, OH, SCH_3 or a reactive esterified OH group, and

A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms or benzyl,

to give [(5-aminocarbonyl-1-methyl-3-propyl-1*H*-pyrazol-4-ylcarbamoyl)-methoxy]acetic acid A ester ("Z7B"),

where

A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms or benzyl,

subsequently

h) "Z7" is converted into (7-oxo-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]-pyrimidin-5-ylmethoxy)acetic acid ("Z8") by cyclisation,

then

i) "Z8" is converted into (7-oxo-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]-pyrimidin-5-ylmethoxy)acetic acid A ester ("Z9"),

where

A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms or benzyl,

subsequently

j) "Z9" is converted into (7-chloro-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-ylmethoxy)acetic acid A ester ("Z10"),

where

A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms or benzyl,

by oxygen-chlorine exchange,

subsequently

k) "Z10" is reacted with 3-chloro-4-methoxybenzylamine to give [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]-pyrimidin-5-ylmethoxy]acetic acid A ester ("Z11"),

where

A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms or benzyl,

and finally

l) "Z11" is hydrolysed to give [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy]acetic acid ("Z12").

3. Compounds selected from the group consisting of

a) [(5-aminocarbonyl-1-methyl-3-propyl-1*H*-pyrazol-4-ylcarbamoyl)-methoxy]acetic acid;

b) [(5-aminocarbonyl-1-methyl-3-propyl-1*H*-pyrazol-4-ylcarbamoyl)-methoxy]acetic acid A ester,
where
A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms
or benzyl;

c) (7-oxo-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl-methoxy)acetic acid;

d) (7-oxo-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl-methoxy)acetic acid A ester,
where
A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms
or benzyl;

e) (7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl-methoxy)acetic acid A ester,
where
A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms
or benzyl;

f) [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy]acetic acid A ester,
where
A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms
or benzyl;

g) [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy]acetic acid,
and salts and solvates thereof.

4. Compounds according to Claim 3, selected from the group consisting of

a) ethyl [(5-aminocarbonyl-1-methyl-3-propyl-1*H*-pyrazol-4-ylcarbamoyl)methoxy]acetate;

b) ethyl (7-oxo-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl-methoxy)acetate;

c) ethyl (7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl-methoxy)acetate;

d) ethyl [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy]acetate;

and salts and solvates thereof.

INTERNATIONAL SEARCH REPORT

national Application No
PCT/EP 01/15372

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 C07D231/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 18004 A (CHRISTADLER MARIA ;MERCK PATENT GMBH (DE); BEIER NORBERT (DE); JON) 15 March 2001 (2001-03-15) claims 1,3; examples 1-7	1-4
A	US 4 666 908 A (HAMILTON HARRIET W) 19 May 1987 (1987-05-19) column 4, line 45 -column 5, line 40 scheme I and II	1-4

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

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'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 April 2002	11/04/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Samsam Bakhtiary, M

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DUMAITRE B ET AL: "SYNTHESIS AND CYCLIC GMP PHOSPHODIESTERASE INHIBITORY ACTIVITY OF A SERIES OF 6-PHENYLPYRAZOLOU3,4-DPYRIMIDONES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 39, no. 8, 1996, pages 1635-1644, XP000651134 ISSN: 0022-2623 page 1635, right-hand column; figure 1 ---	1-4
A	US 6 130 223 A (CHRISTADLER MARIA ET AL) 10 October 2000 (2000-10-10) claim 1 ---	1-4
A	DE 197 52 952 A (MERCK PATENT GMBH) 2 June 1999 (1999-06-02) claim 1 -----	1-4

INTERNATIONAL SEARCH REPORT

Information on patent family members

National Application No
PCT/EP 01/15372

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0118004	A	15-03-2001	DE	19942474 A1	15-03-2001
			AU	7279300 A	10-04-2001
			WO	0118004 A2	15-03-2001
US 4666908	A	19-05-1987	EP	0201188 A2	17-12-1986
			JP	61236778 A	22-10-1986
US 6130223	A	10-10-2000	DE	19644228 A1	30-04-1998
			AU	726639 B2	16-11-2000
			AU	4945097 A	15-05-1998
			BR	9712652 A	26-10-1999
			CZ	9901422 A3	14-07-1999
			WO	9817668 A1	30-04-1998
			EP	0934321 A1	11-08-1999
			HU	9904680 A2	28-05-2000
			JP	2001502342 T	20-02-2001
			NO	991951 A	17-06-1999
			PL	332970 A1	25-10-1999
			SK	50299 A3	13-03-2000
			ZA	9709516 A	12-05-1998
DE 19752952	A	02-06-1999	DE	19752952 A1	02-06-1999
			AU	742433 B2	03-01-2002
			AU	1962599 A	16-06-1999
			BR	9815409 A	24-10-2000
			CA	2311922 A1	10-06-1999
			CN	1306534 T	01-08-2001
			CZ	20001962 A3	16-01-2002
			WO	9928325 A1	10-06-1999
			EP	1036078 A1	20-09-2000
			HU	0100488 A2	28-09-2001
			JP	2001525325 T	11-12-2001
			NO	20002702 A	26-05-2000
			PL	341156 A1	26-03-2001
			SK	7772000 A3	11-12-2000
			ZA	9810845 A	26-05-1999